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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,834	RATAIN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/30/2005

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1, 2, 5-108* is/are pending in the application.

4a) Of the above claim(s) *19-40,42,44-65,67 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-18,41,43,66,68-71 and 94-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed March 30, 2005. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. It is noted that Applicant elected Group I, claims 1-100, without traverse in the reply filed on July 19, 2004. Further, Applicant elected the species of epirubicin. The claims readable on the elected species are claims 1, 2, 5-18, 41, 43, 66, 68-71 and 94-100. Claims 19-40, 42, 44-65, 67, and 101-108 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-18, 41, 43, 66, 68-71 and 94-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining the dose of morphine to administer to a patient wherein the method comprises obtaining a sample nucleic acid from a patient, analyzing the sample nucleic acid directly for the presence of a polymorphism in the UGT2B7 gene, detecting the presence or absence of a T or C polymorphism at position -161 of the UGT2B7 gene or the presence of a TC or AT polymorphism at positions 801-802 of the UGT2B7 gene

and determining the appropriate dose of morphine to administer to the patient based on the presence or absence of one of said polymorphisms and while enabling for general methods of assaying for UGT2B7 glucoronidation of epirubicin, does not reasonably provide enablement for all methods for determining a dose of any UGT2B7-glucoronidated drug by assaying for the level of UGT2B7 activity, assaying for the activity of UGT2B7 or assaying for the presence of any polymorphism in the UGT2B7 gene or other unstated gene as a means for determining the dose of any UGT2B7-glucoronidated drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for determining the dose of any UGT2B7-glucoronidated drug wherein the methods comprise determining the level or activity of UGT2B7 and determining the dose of the drug based on the activity or level of UGT2B7. The claims include methods in which UTG2B7 is directly assayed for enzyme activity, for the level of protein or mRNA, or for the presence of any first polymorphism associated with UTG2B7 activity or for any second polymorphism linked to said first

polymorphism. The claims further encompass methods for evaluating the risk of toxicity of any UGT2B7-glucoronidated drug by directly or indirectly determining the nucleotide sequence at position –161 of the UGT2B7 gene; methods for screening for glucoronidation activity by identifying any polymorphism that correlates with glucoronidation activity; and methods for predicting the degree of an epirubicin-induced toxicity in a cancer patient by directly or indirectly determining the nucleotide sequence at position –161 of the UGT2B7 gene.

The specification teaches that UGT's catalyze the glucoronidation of distinct substrates. The specification also teaches that there is considerable variability between individual's with respect to their glucoronidation activities and suggests that the presence of polymorphisms in UGT genes may influence glucoronidation activity. In Table 1, the specification discloses 15 polymorphisms in the UGT2B7 gene. Two additional polymorphisms are disclosed in Table 6. The specification (see Example 11) also teaches that the –161 promoter polymorphism is in complete linkage disequilibrium (LD) with the +801/+802 polymorphisms, which lead to a His > Tyr mutation at amino acid position 268. Further, the specification (see, e.g., page 110) teaches that the T/T –161 genotype is associated with increased glucoronidation of morphine to M6G and M3G as compared to the C/C –161 genotype. Thereby, the specification has established an association between the –161 T/C polymorphism and glucoronidation of morphine. However, with respect to the cancer therapeutic epirubicin, the specification (page 101) teaches that "Differences in epirubicin glucoronidation between UGT2B7(H) and UGT2B7(Y) variants were not observed." Accordingly, the specification has not

established a correlation between glucoronidation of epirubicin and any particular polymorphism in the UGT2B7 gene or changes in the level or activity of UGT2B7.

The specification is enabling only for methods in which a dosage of morphine is selected for a patient based on the presence or absence of a T or a C at position –161 of the UGT2B7 gene or the presence or absence of TC or AT at positions +801/+802 of the UGT2B7 for the following reasons:

The results obtained with morphine glucoronidation cannot be extrapolated to other UGT2B7-glucoronidated drugs because the activity of UGT2B7 variants differs with respect to the drug and with respect to the particular UGT2B7 variant. This finding is highlighted by the teachings in the specification that the UGT2B7(H) and UGT2B7(Y) variants (i.e., the polymorphisms at positions –161 and at +801/+802) do not show differences in their ability to glucoronidate epirubicin, while these variants do appear to show differences in their ability to glucoronidate morphine.

The ability to determine an association between UGT2B7 levels/activity and the presence of specific polymorphisms is highly unpredictable. Again, the effect of a polymorphism appears to be substrate-dependent. Further, there is no clear association between any particular polymorphism and glucoronidation levels or activity. The specification does not teach any specific polymorphisms which alter the level of UGT2B7 protein or mRNA. Nor, does the specification teach any polymorphism which is associated with an increase or decrease of UGT activity with respect to all UGT2B7 substrates. The specification teaches only one set of polymorphisms – i.e., the –161

and +801/+802 polymorphisms – which are associated with the degree of glucoronidation of morphine. No additional polymorphisms associated with morphine glucoronidation have been disclosed and no polymorphisms are disclosed in the specification which are clearly associated with any other UGT2B7 substrates.

With respect to epirubicin in particular, no working examples are provided in the specification in which a dosage of epirubicin is selected based on differences in the level of UGT2B7 mRNA or protein, differences in the level of UGT2B7 activity, or the presence or absence of a polymorphism. The specification has not established that individual's possess different levels of UGT2B7 mRNA or proteins or have different UGT2B7 activity levels which clearly correlate with the efficiency of glucoronidation of epirubicin. The specification does not teach how to determine the appropriate dosage of epirubicin to be administered to a patient based on the level or activity of UGT2B7 because the specification has not established that UGT2B7 levels and activities vary between patients and that these changes alter the level of epirubicin glucoronidation. Thereby, the specification does not provide sufficient guidance as to how to determine the dosage of epirubicin by assaying for the presence of a polymorphism or by assaying for epirubicin mRNA or protein levels or enzyme activity.

The unpredictability of determining an association between UGT2B7 level/activity and the occurrence of a polymorphism is supported by the teachings in the art. For example, Bhasker (Pharmacogenetics (2000) 10: 679-685) teaches that there was no observed differences between the rates of glucoronidation of androsterone, menthenol and morphine with respect to the UGT2B7(H) and UGT2B7(Y) variants (see page 683).

Bhasker (page 684) concludes that "His268Tyr substitution minimally influences enzyme activity, and the clearances of drugs and other compounds metabolized by UGT2B7 would not be expected to vary substantially with genotype. However, a significant effect on specific substrates cannot be discounted." Further, Bhasker (page 684) emphasizes that "Although the UGT2B7 polymorphism described here may not be associated with altered enzyme activity, the results highlight the need to consider racial variability in assessing the consequences of UGT polymorphisms."

Additionally, Innocenti et al (of which the present inventors are co-authors; Drug Metabolism and Disposition. 2001. 29: 686-692; see abstract) states that "The reported tyrosine to histidine polymorphism in UGT2B7 does not alter the formation rate of epirubicin glucoronide, and *undiscovered genetic polymorphisms in UGT2B7 might change the metabolic fate of this important anticancer drug"* (emphasis added). Accordingly, at the time the invention was made, and as of 2001, an association between epirubicin glucoronidation and the presence of any particular polymorphism in the UGT2B7 gene had not yet been discovered.

Additionally, Toide (Drug Metabolism and Disposition (2002) 30: 613-615) supports the finding that it is unpredictable as to whether UGT2B7 mRNA levels are associated with changes in enzyme activity. Toide (see abstract) reports that "A novel point mutation (-253G to A) found in this study did not affect the level of UGT2B7 mRNA in subjects." Toide (page 615) found that "interindividual variation in the UGT2B7 enzyme activity occurred by the variation in the amounts of HNF-1a mRNA" rather than as a result of variation in the amount of UGT2B7 mRNA.

In view of the high level of unpredictability in the art as set forth above, an association between a UGT2B7 polymorphism or UGT2B7 activity or protein or mRNA levels can only be established through extensive experimentation. Such experimentation requires analyzing the UGT2B7 gene for the presence of a known or unknown polymorphism, determining whether the polymorphism is directly associated with a change in the level or activity of glucoronidation of a specific UGT2B7 substrate or by determining whether the polymorphism is indirectly associated with UGT2B7 levels or activity by screening for the presence of the polymorphism in a population showing a difference in their ability to glucoronidate specific substrates, and trying to determine which, if any, of the identified polymorphisms are directly or indirectly associated with a change in UGT2B7 levels or glucoronidation of specific substrates. There is no means to predict a priori which of the multitude of possible polymorphisms in UGT2B7 genes or genes linked thereto would be associated with any one or more of the various UGT2B7 substrates. Accordingly, such, random, trial-by-error experimentation is considered to be undue.

Further, it is noted that the claims are written in a manner such that they do not require the direct analysis of any particular polymorphism. Rather, the claims encompass indirectly inferring the presence of a polymorphism or the level of activity of UGT2B7 or the expression of UGT2B7 by assaying for the presence of some unstated polymorphism that may be linked to whatever degree to some other stated or unstated polymorphism, by performing some unspecified activity assay or by determining the level of some unspecified mRNA or protein. However, the specification has not taught a

representative number of polymorphisms, activity assays or proteins or mRNAs which can be analyzed to predictably determine the level of UGT2B7 activity to a specific substrate. The specification has taught only an association between the occurrence of the –161 polymorphism and the +801/+802 polymorphisms. No additional polymorphisms in complete linkage disequilibrium with –161 or +801/+802 have been identified. Nor has the specification disclosed any additional UGT2B7 polymorphisms in linkage disequilibrium with other UGT2B7 polymorphisms or polymorphisms present in other unspecified genes. No specific guidance has been provided in the specification as to what would be the identity of other polymorphism in linkage disequilibrium with an a polymorphism correlated with glucoronidation activity or the identity of other mRNAs or proteins which could be analyzed to provide information on the level or activity of UGT2B7.

The claims also include methods of determining a dose of a UGT2B7-glucoronidated drug by assaying for glucoronidation activity in general. However, as discussed above, it is expected that variants of UGT2B7 may have different activities with respect to different substrates. Thereby, assaying an individual's UGT2B7 activity in general will not provide an accurate reflection of that individual's capacity to glucoronidate a specific UGT2B7 substrate. To determine an appropriate dosage of a UGT2B7-glucoronidated drug requires determining the level of UGT2B7 activity in an assay using that specific drug as a substrate.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed

invention without undue experimentation" (*In re Wright* 990 F.2d 1557, 1561). *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement." In the instant case, the scope of the claims does not bear a reasonable correlation to the scope of enablement because the specification has established an association only between one specific UGT2B7 substrate, i.e. morphine, and one specific set of polymorphisms, i.e., the –161 and +801/802 polymorphisms. The specification does not teach a correlation between a representative number of substrates and polymorphisms or UGT2B7 variants having increased or decreased expression levels or activities. In view of the high level of unpredictability in the art and the lack of specific guidance provided by the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the response filed March 30, 2005, Applicants traversed this rejection by noting that page 104 of the present specification teaches that "Since morphine is glucoronidated by UGT2B7 (Coffman et al, 1997), correlation between epirubicin and

morphine glucoronidation rates was assessed in 47 normal liver microsomes." However, page 104 of the specification and figure 4 teach glucoronidation of epirubicin by UGT2B7 in general. These teachings do not address the -161 UGT2B7 polymorphism and particularly do not address the relationship between the –161 UGT2B7 polymorphism and glucoronidation of epirubicin.

The response states that the specification at page 109 teaches that the –161 polymorphism in UGT2B7 is correlated with conversion of morphine to either M3G or M6G. Based on this disclosure, the response argues that it would not require undue experimentation to practice the invention using epirubicin "because of the correlation data." However, the specification does not in fact teach a correlation between the –161 UGT2B7 polymorphism and glucoronidation of epirubicin. Morphine and epirubicin are distinct chemical compounds and the results obtained with one compound cannot be extrapolated to other compounds in view of the unpredictability in the art as set forth in the above rejection.

Importantly, Applicant's response does not address a key aspect of the rejection – i.e., the fact that the specification (page 101) specifically states that "Differences in epirubicin glucoronidation between UGT2B7(H) and UGT2B7(Y) variants were not observed." The present specification (e.g., pages 15 and 108) teaches that the –161 polymorphism is in complete linkage disequilibrium with the +802 (UGT2B7H/Y) polymorphism and thereby the specification concludes that the presence of the –161 polymorphism can be detected by detecting the +802 polymorphism. Accordingly, the teachings of the specification when taken as a whole indicate that the –161 UGT2B7

polymorphism is also not correlated with epirubicin glucoronidation and thereby the presence of this polymorphism cannot be used to determine the appropriate dosage of epirubicin.

The response states that the teachings of Bhasker, Innocenti and Toide are not applicable to the present invention because these references do not teach the polymorphism at position –161. It is asserted that the present claims are limited to detecting the polymorphism at position –161. However, the present claims are not in fact limited to methods which detect the –161 polymorphism. Rather, as discussed at length within the rejection, the claims encompass indirectly evaluating the nucleotide present at nucleotide position –161 of the UGT2B7 gene as a means for determining the activity or expression level of UGT2B7. The claims (e.g., claim 12) specifically recite that the –161 polymorphism is detected by assaying for the nucleotide present at position +801 or +802. The claims also encompass detecting any polymorphism in linkage disequilibrium with the –161 polymorphism as a means for determining the nucleotide sequence at position –161. Additionally, the claims include evaluating the nucleotide at position –161 by assaying for enzyme activity, by assaying mRNA levels and by assaying for mutations in other genes. Thereby, the claims are NOT limited to methods which determine the dosage of epirubicin by directly determining the nucleotide present at nucleotide position –161 of the UGT2B7 gene. Importantly, the specification (e.g., page 15) teaches that the +802 polymorphism is in full linkage disequilibrium with the –161 polymorphism and thereby the specification concludes that the results obtained with the +802 polymorphism can be fully extrapolated to the –161

polymorphism. However, again, the specification (page 101) specifically teaches that the +802 (UGT2B7His/Tyr) mutation is not correlated with epirubicin glucoronidation. Further, Innocenti was cited because this reference confirms the lack of an association between UGT2B7 polymorphisms and glucoronidation of epirubicin. Specifically, this reference states that "The reported tyrosine to histidine polymorphism in UGT2B7 does not alter the formation rate of epirubicin glucoronide, and *undiscovered genetic polymorphisms in UGT2B7 might change the metabolic fate of this important anticancer drug"* (emphasis added).

The response states that the findings of Toide regarding mRNA levels are not relevant to the present claims because the present results are based on enzyme activity and not on mRNA levels. This argument is not persuasive because the claims are not limited to methods which directly detect the polymorphism at position –161 or methods which evaluate enzyme activity. In fact, the present claims specifically include determining the expression level of UGT2B7 (i.e., determining the mRNA levels of UGT2B7). Accordingly, the findings of Toide are relevant to the broadly claimed invention because Toide establishes the unpredictability in assaying for a polymorphism indirectly by assaying for mRNA levels since this reference teaches that mRNA levels did not correlate the –253G/A UGT2B7 polymorphism although this polymorphism did correlate with variations in enzyme activity. Also, the teachings of Bhasker et al are relevant to the present invention as it is broadly claimed because this reference teaches that the +802 (UGT2B7His/Tyr) mutation is not correlated with the glucoronidation of

other "UGT2B7-glucoronidated drugs," including androsterone, methenol, and morphine.

Lastly, it is noted that the response refers to the polymorphism at position –160 and page 109 of the specification also discusses a polymorphism at position –160. However, the present claims and other sections of the specification (e.g., page 110) refer to a polymorphism at position –161. Clarification of the position of the UGT2B7 polymorphism is required.

4. Claims 10, 43, 66, 68-71, and 94-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 10 is indefinite and confusing over the recitation of "identification of a second thymine," "identification of a second cytosine," and "identification of a residue different than the residue in the first promoter" because the claim does not previously refer to a first thymine, cytosine or residue in the promoter. Thereby, it is unclear as to how claim 10 is intended to be further limiting from claim 3 and it is unclear as to what would constitute a residue that is different from the residue in the first promoter. Also, claim 10 is further indefinite because it now depends from a cancelled claim.

RESPONSE TO ARGUMENTS:

In the response of March 30, 2005, Applicants state that this rejection has been rendered moot by the cancellation of claim 10. However, claim 10 has not been cancelled. Accordingly, the above rejection is maintained.

B. Claims 68-71 are indefinite. The claims are drawn to a method for evaluating the risk for toxicity from a UGT2B7-glucoronidated drug in a patient. The claims recite a final step of determining the level of UGT2B7 activity or expression by determining the nucleotide sequence at position –161 in one UGT2B7 gene. However, the claims do not clarify how the step of determining UGT2B7 activity or expression results in the evaluation of the risk of toxicity. There is no nexus between the preamble of the claim and the final process step. Thereby, it is unclear as to whether the method is intended to be one for evaluating the risk for toxicity from a UGT2B7-glucoronidated drug in a patient or one for determining the activity or expression of UGT2B7.

RESPONSE TO ARGUMENTS:

In the response of March 30, 2005, Applicants state that the claims have been amended to clarify that the level of UGT2B7 activity or expression is determined by determining the nucleotide present at position –161. However, this amendment does not overcome the above rejection. The claims do not state how determining the enzyme level or activity or determining the nucleotide at position –161 results in the evaluation of the risk of toxicity of UGT2B7-gluconidated drug. The claims fail to recite a clear nexus between the preamble of the claims and the process steps of the claims. Thereby, it remains unclear as to whether the claims are limited to methods which determine the level of UGT2B7 activity or expression or the nucleotide present at position –161 or methods which evaluate the risk of toxicity of UGT2B7-gluconidated drug.

C. Similarly, claims 94-98 are indefinite because the claims are drawn to methods for screening an individual for glucoronidation activity, yet recite a final step of identifying the nucleotide sequence of a polymorphism. The claims do not recite a clear nexus between identifying the nucleotide sequence of a polymorphism and determining glucoronidation activity. It is thereby unclear as to whether the claims include methods which merely determine a UGT2B7 nucleotide sequence, or whether the claims are intended to encompass methods of screening for glucoronidation activity.

RESPONSE TO ARGUMENTS:

In the response of March 30, 2005, Applicants traverse this rejection for the same reasons stated in "B" above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

D. Claim 99 is indefinite. The claim is drawn to a method for prescribing a dose of a UGT2B7-glucoronidated drug. However, the final step is one for determining the level of UGT2B7 activity. The claim does not recite a clear nexus between the preamble and final process step and it is unclear as to how determining the level of UGT2B7 results in the prescription of a dose of a UGT2B7-glucoronidated drug.

RESPONSE TO ARGUMENTS:

In the response of March 30, 2005, Applicants state that the amount of drug to be prescribed to a patient may involve considering toxicity issues. It is asserted that the meaning of the claim is clear because the specification teaches that dosage of a drug may be altered to reduce side effects. This argument has been fully considered but is

not persuasive. While the claims are read in light of the specification, limitations from the specification are not read into the claims. The rejection is maintained because the claims themselves do not recite a clear nexus between the steps of determining the level of UGT2B7 activity and prescribing the dose of the drug. There is nothing in the claim itself which indicates how the level of UGT2GB7 activity is to be used to accomplish the claim objective of prescribing a dose of a drug. Thereby, it remains unclear as to whether the claimed method requires only the steps of obtaining a sample and determining the level of UGT2B7 activity in a sample or if the claim actually requires prescribing a dose of a drug to a patient. In the later case, the claim does not clarify the relationship between determining the UGT2B7 activity and prescribing a dose of a drug to a patient. Thereby, one cannot ascertain the meets and bounds of the claimed invention.

E. Claim 100 is indefinite. The claim is drawn to a method for predicting the degree of an epirubicin-induced toxicity. However, the claim recites a final step of determining the nucleotide sequence at position –161. The claim does not recite a clear nexus between the preamble and the final process step and it is unclear as to how determining the nucleotide sequence at position –161 accomplishes the objective set forth in the preamble of the claim of predicting the degree of epirubicin-induced toxicity. Thereby, it is unclear as to whether the claim is intended to be limited to methods for predicting the degree of an epirubicin-induced toxicity or methods for determining the nucleotide sequence at position

–161.

RESPONSE TO ARGUMENTS:

In the response of March 30, 2005, Applicants state that because the specification teaches that the main detoxifying pathway for epirubicin is the formation of epirubicin glucoronide and because the specification teaches that UGT2B7 mediates glucoronidation of UGT2B7-glucoronidated drugs, it is clear that the claim is limited to methods for predicting the degree of epirubicin-induced toxicity. This argument has been fully considered but is not persuasive. Again, while claims are read in light of the specification, teachings from the specification are not read into the claims. The claims do not recite a clear nexus between the steps of determining the level of UGT2B7 activity or expression and determining the degree of epirubicin-induced toxicity. The claim does indicates how the level of UGT2GB7 activity or expression is to be used to accomplish the claim objective of determining the degree of epirubicin-induced toxicity. Thereby, it remains unclear as to whether the claimed method requires only the steps of obtaining a sample and determining the level of UGT2B7 activity or expression in a sample or if the claim actually requires determining the degree of epirubicin-induced toxicity. In the later case, the claim does not clarify the relationship between determining the UGT2B7 activity or expression and determining the degree of epirubicin-induced toxicity. Thereby, one cannot ascertain the meets and bounds of the claimed invention.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS:

F. Claims 43 and 66 are indefinite over the recitation of "determining the activity of UGT2B7 in a patient according to the method of claim 1" because claim 1 is not limited to a method for determining the activity of UGT2B7. Rather, claim 1 is drawn to a method for determining a dose of a UGT2B7-glucoronidated drug. Accordingly, it is not clear as to how claims 43 and 66 are intended to be further limiting from claim 1 and it is unclear as to what is intended to be the relationship between claim 1 and claims 43 and 66.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00

PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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June 6, 2005

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